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A randomized, placebo-controlled trial on the effects of soy protein containing isoflavones on quality of life in postmenopausal women

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Abstract

Objective: Postmenopausal estrogen decline is implicated in several age-related physical and psychological changes in women, including decreases in perceived quality of life (QoL). A number of trials with hormone therapy showed beneficial effects of the intervention on parameters of quality of life. However, because of known or suspected serious side-effects of conventional hormone therapy there is a need for alternatives.

Design: We conducted a double-blind randomized placebo-controlled trial with soy protein, containing 52 mg genistein, 41 mg daidzein, and 6 mg glycitein (aglycone weights), or milk protein (placebo) daily for 1 year. For this trial, we recruited 202 postmenopausal women aged 60 to 75 years.

Results: At baseline and at final visit, participants filled in the Short Form of 36 questions (SF-36), the Questionnaire on Life Satisfaction Modules (QLS^M), and the Geriatric Depression Scale (GDS). For the placebo group scores on all dimensions of the SF-36 and the QLS^M decreased during the intervention year, except for the dimension "role limitations caused by physical problems." The soy group showed increases on two dimensions of the SF-36 ("social functioning" and "role limitations caused by physical problems") and on one dimension of the QLS^M. There were however no statistically significant differences in changes of scores between the two intervention groups. For the GDS similarly, no significant differences were found between the groups.

Conclusion: In conclusion, the findings in this randomized trial do not support the presence of a marked effect of soy protein substitution on quality of life (health status, life satisfaction, and depression) in elderly postmenopausal women.

Key Words: Soy isoflavones – Health status – Life satisfaction – Depression – Postmenopausal women – Randomized trial.

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Estrogen deprivation has been held responsible for physical and psychological changes occurring during menopause. Among these changes are increased incidence of cardiovascular diseases,[1] increased fracture risk,[2,3] and decreased perceived quality of life, including disturbed sleep patterns, mood changes, and vasomotor symptoms.[4] Accordingly, estrogen therapy was expected to prevent chronic diseases and improve quality of life.[5] In the United States, there is widespread belief that postmenopausal hormones may have general positive effects on the health of older women. However, estrogen therapy is also associated with putative harmful effects, such as increased

incidence of breast cancer,[6,7] endometrial cancer, and venous thromboembolism.[8,9] Whether the net effect of postmenopausal hormones is to increase life expectancy is still unclear.[7] However, prolonging life is not the only consideration for women and doctors in making decisions about chronic medication; quality of life may be equally or more important.

Phytoestrogens may offer an alternative for hormone therapy (HT), sharing the benefits, but not the risks. Phytoestrogens are derived from plants and have a nonsteroidal structure that is quite similar to that of estradiol. The three main classes are isoflavones, lignans, and coumestans. Various studies have demonstrated positive effects of phytoestrogens on hot flushes,[10] bone mineral density,[11,12] and cardiovascular disease risk factors[13] without indications for an increased risk of endometrial cancer[14] or breast cancer.[15] However, whether application for a longer period of time or in older postmenopausal women is also useful has still to be proven.

In a randomized placebo-controlled trial we assessed the effects of supplementation of soy protein containing naturally occurring isoflavones for one year on quality of life (health status, life satisfaction, and depression) in postmenopausal women, aged 60 to 75 years.

SUBJECTS AND METHODS

The present study is a double blind, randomized, placebo-controlled trial to assess the effects of soy protein containing naturally occurring isoflavones on bone, vascular aging, cognitive function, quality of life (QoL), and physical performance as discussed in detail previously.[16] Endometrium thickness and mammographical breast pattern were monitored as safety measures.

The number of subjects was based on power calculations for the primary endpoints bone mineral density and cognitive function. The assumptions were $\alpha = 0.05$ and $\beta = 0.20$ and withdrawal of intervention of 25%, resulting in a planned number of subjects of 200 in total. For SF-36 items such as Vitality or General Health Perception, we would be able to find an improvement of 6 to 7 points, or 9%, and for Mental Health an improvement of 5.5 points, or 7%.

Subjects

We recruited postmenopausal women, aged 60 to 75 years, through the national screening program for breast cancer. All had a normal mammogram in the year before enrolment. Subjects were not eligible when they had active renal or liver disease, a history of thromboembolism, a history of carcinoma, current use of HT or use of HT in the 6 months before enrolment, allergy for soy or milk protein, or endometrial thickness larger than 4 mm. Of the 303 subjects who were willing to participate, we had to exclude 101 women for several reasons; the most important being current use of HT (n = 26), history of carcinoma (n = 15), and history of thrombosis (n = 14). Finally, 202 women were enrolled in the trial and randomized to one of two intervention arms.

The Institutional Review Board of the University Medical Center Utrecht, The Netherlands approved the study protocol, and all subjects gave written informed consent.

Intervention

Subjects were randomly assigned to the soy intervention group or the placebo group in random blocks of ten. A list of randomization numbers was computer-generated by personnel not involved in the trial. Each randomization number corresponded with one of the two possible interventions. Randomization numbers were assigned to the subjects in order of enrollment into the trial.

The intervention consisted of 25.6 g soy protein containing 52 mg genistein, 41 mg daidzein, and 6 mg glycitein (aglycone weights) (Solae brand soy protein; The Solae Company, St Louis, MO) as a powder. All three isoflavones were naturally occurring. The total serving size of the product was 36.5 g. Placebo was an identical-looking and tasting powder consisting of 36.5 g of milk protein (DuPont Protein Technologies, St. Louis, MO). The supplements could be mixed with foods or beverages. The duration of the intervention was 12 months, in which supplements had to be taken daily. Baseline measurements included a validated semiquantitative food frequency questionnaire on habitual diet in the year before enrollment,[17] which was slightly modified to fully capture phytoestrogen intake.

At each control visit, except for the 9-months visit, subjects filled in a food frequency questionnaire again covering the months between the last and the current visit.

Compliance was checked by assessing plasma genistein levels in the final visit blood sample.

During the intervention period, 49 subjects (24 subjects in the placebo group and 25 subjects in the soy group) (24%) dropped out for several reasons, notably gastrointestinal complaints and distastefulness of the supplement. Mean duration of participation of the dropouts was 96 days (range: 4-285 d). We performed a close out visit when a subject participated for at least 1 month. Of the subjects who dropped out, 35 fulfilled this criterion and 22 of them were willing and able to undergo a final visit (9 from the placebo group and 13 from the soy group).

Quality of life

At baseline and at the end of the intervention period, quality of life (health status, life satisfaction, and depression) was measured using the Short Form of 36 questions (SF-36), the Questions on Life Satisfaction Modules (QLS^M), and the Geriatric Depression Scale (GDS).

The SF-36 is a self-administered questionnaire containing 36 items that measure the perception of health on eight dimensions: physical functioning, social functioning, role limitations because of physical problems, role limitations because of emotional problems, mental health, vitality, pain, and general health perception. The eight dimensions cover functional status, well-being and overall evaluation of health. For each dimension, the possible scores range from 0 to100, with higher scores indicating a better quality of life.[18-20]

The QLS^M we used consists of three modules: General Life Satisfaction (QLS^M-A), Satisfaction with Health (QLS^M-G), and a disease-specific module on growth-hormone deficiency (QLS^M-H), that is also very appropriate for use in sex steroid deficiency.[21]

Each module comprises two parts. In the first part, subjects are asked to rate the importance of each item within the module and in the second part, the subjects are asked about the degree of satisfaction with each item. In this way, individual weighting of the items is realized. The first two modules include eight items, the third module, in the version we used, includes 16 items. Scores on the first two modules can vary between −96 and 160 and on the last module between −192 and 320. The questionnaire produces total scores for each module separately.[22]

The GDS is a self-rated screening instrument especially designed to measure depression in the elderly.[23] The GDS consists of 30 items with only two possible answers (yes/no). Of those 30 questions, 20 are indicative of depression when answered positively and the other 10 when answered negatively. Scores can range from 0 to 30 with subjects without depression having lower scores.

We asked participants to fill in the forms at home one day before their visit at our outpatient clinic. On the day of the visit the research nurses checked the forms for missing answers or inconsistencies. The scoring of the questionnaires was performed according to the published criteria.

Laboratory measurements

Plasma genistein levels were measured using Labmaster TR-FIA kits (Turku, Finland). Fluorescence was measured on the Wallac Victor 2 model 1420 fluorometer (Turku, Finland). Data were analyzed using GraphPad Prism software (GraphPad Software Inc, San Diego, CA). Intra-assay and inter-assay CVs were 2.2% and 14.8%, respectively.

Data analysis

Data were analyzed according to the intention-to-treat principle for those who had two measurements including baseline. Linear regression analysis was used with baseline-to-final visit change in questionnaire scores as dependent variable and group allocation as independent variable. Results are given including a 95% CI. We also performed subgroup analysis based on baseline QoL scores. The study population was divided into two groups. As cutoff point, we used the median of the scores on the different dimensions. When the median score was equal to the maximum score, we used the mean.

All analyses were performed using the SPSS 9.0 for Windows statistical package (SPSS Inc, Chicago, IL).

RESULTS

Baseline characteristics of participants are listed in Table 1. Despite randomization, the number of current smokers was somewhat higher in the soy group. The other features were similarly distributed between both groups. Table 2 represents the baseline scores of the SF-36, the QLS^M, and the GDS. Also for the baseline scores on the questionnaires, there were no significant differences between both intervention groups.

Table 3 shows the scores at the end of intervention, the change in scores compared to baseline expressed as a percentage and the difference in change between the

TABLE 1. *Baseline characteristics of participants*

	Intervention	
	Soy protein mean (SD) n = 100	Placebo mean (SD) n = 102
Mean age (y)	66.6 (4.8)	66.8 (4.7)
BMI (kg/m^2)	26.4 (4.1)	26.0 (3.4)
Systolic blood pressure (mm Hg)	138.5 (18.5)	142.0 (20.5)
Diastolic blood pressure (mm Hg)	74.5 (11.5)	76.0 (13.5)
Age at menopause (y)	48 (6)	49 (4)
Years postmenopausal (y)	18.5 (7.5)	18.6 (6.0)
Fertile years (y)	34.5 (6.5)	35.5 (4.5)
	n (%)	n (%)
Ever use of estrogens	22 (22.2%)[a]	23 (22.5%)[a]
Current smoking	19 (19.0%)	13 (12.7%)
Former smoking	33 (33.0%)	34 (33.3%)

[a]Not known for all subjects.

TABLE 2. *Baseline results of the separate dimensions of the SF-36 and QLS^M and the GDS*

Questionnaires	Soy protein mean (SD) n = 100	Placebo mean (SD) n = 102
SF-36		
Physical functioning	82 (19)	84 (15)
Social functioning	90 (16)	89 (16)
Role limitations caused by physical problems	89 (23)	88 (22)
Role limitations caused by emotional problems	95 (16)	95 (14)
Mental health	79 (13)	79 (13)
Vitality	72 (16)	70 (16)
Pain	82 (20)	79 (19)
General health perception	70 (15)	70 (15)
QLS^M		
QLS^M-A	77 (23)	77 (27)
QLS^M-G	79 (31)	77 (30)
QLS^M-H	95 (52)	100 (50)
GDS	4.9 (4.0)	5.0 (5.1)

two intervention groups. For both the SF-36 and the QLS^M, a decrease in scores indicates a decrease in perception of quality of life.

For the placebo group, the scores on all dimensions of the SF-36 were lower after 1 year except for the dimension "role limitations caused by physical problems" that appeared to remain stable. The soy intervention group showed a decrease in scores on four dimensions, two dimensions were stable, and two dimensions showed an increase. The baseline-to-final visit changes in mean scores on the eight dimensions did not differ statistically significantly among the intervention groups.

For the SF-36, we also calculated a physical summary score and a mental summary score.[24] The difference in change for the physical summary score was 0.05 (95% CI −1.97, 2.08; $P = 0.96$) and for the mental summary score 0.69 (95% CI −2.08, 3.46; $P = 0.62$).

Subgroup analysis by the baseline scores on the SF-36 showed no difference in effect of the intervention.

For the QLS^M, the placebo group demonstrated a decrease in scores on all three dimensions (−1 point on QLS^M-A, −1 on QLS^M-G, and −3 on QLS^M-H), and the soy intervention group only had a slight increase on the QLS^M-A (+1 point). Again there were no significant differences in change of scores between the soy intervention group and the placebo group (Table 3).

Results of both the SF-36 and the QLS^M were consistent with regard to general health perception as to be expected.

For the GDS, scores and changes in scores were virtually identical in both intervention groups. Scores in the placebo group were 5.01 at baseline and 5.76 at the final visit (change 0.75). For the soy group, scores were 4.87 and 5.38, respectively (change 0.51). Difference in change 0.24 (95% CI −1.33, 0.84; $P = 0.66$) (Table 3).

Plasma genistein levels were markedly different between the intervention group and the placebo group (1259 ± 1610 and 55 ± 101 nM, respectively, P for difference <0.001), indicating that compliance was good.

DISCUSSION

The present study did not demonstrate an overall beneficial effect of a 1-year supplementation of soy protein containing naturally occurring isoflavones on

TABLE 3. *Differences in baseline-to-final visit change in scores*

Modules	Placebo group (n = 102) Final score	Placebo group (n = 102) % change	Soy group (n = 100) Final score	Soy group (n = 100) % change	[a]	95% CI	P
SF-36							
Physical functioning	83	−1	82	0	0.87	−2.38; 4.13	0.60
Social functioning	87	−2	91	+1	2.02	−3.85; 7.88	0.50
Role limitations caused by physical problems	88	0	91	+2	2.29	−7.86; 12.43	0.66
Role limitations caused by emotional problems	94	−1	95	0	1.69	−7.87; 11.25	0.73
Mental health	75	−5	77	−3	2.22	−1.63; 6.07	0.26
Vitality	69	−1	71	−1	−0.09	−4.22; 4.03	0.96
Pain	78	−1	80	−2	−1.46	−6.89; 3.97	0.60
General health perception	69	−1	69	−1	1.30	−2.68; 5.27	0.52
QLS^M							
General life satisfaction	76	−1	78	+1	1.35	−5.30; 8.01	0.69
Satisfaction with health	76	−1	73	−8	−6.36	−15.09; 2.38	0.15
Satisfaction hormone-specific	97	−3	92	−3	0.35	−15.47; 16.17	0.97
GDS	5.8	15	5.4	10	−0.24	−1.33; 0.84	0.66

[a]Represents the difference in change of scores for the soy group relative to the placebo group.

quality of life in postmenopausal women. Strengths of the study include the duration of the study, the large number of participants and the reasonable number of drop-outs. Moreover, we made use of well-established measurements of quality of life.

There are however also some limitations. Our research population consisted of healthy women without major complaints. This is reflected in the mean scores of the SF-36 at baseline (Table 2): women in our study appeared to rate their health status high at all dimensions of the SF-36 at baseline. Consequently, it may be unrealistic to expect a further marked increase in health status.

Despite the fact that all questionnaires were checked, the QLS^M contained three questions that led to a number of missing answers. Some women, although never exceeding 10%, were not willing to answer questions about sexual functioning and partnership. When imputing missing answers with either the best possible answer for the one intervention group or the worst possible answer for the other intervention group, results did not change. Thus we decided not to formally impute the missing data, moreover, because it could be argued that the missing items were not at random.[25,26]

There are numerous instruments measuring quality of life, all differing in content and construct and there is no gold standard. Previous studies assessing the relation between use of HT and quality of life in postmenopausal women all used different questionnaires with only a little overlap.[27–32] It is difficult to determine to what extent results of studies using different questionnaires can be compared. Decrease in estrogen levels might, as mentioned before, lead to climacteric symptoms, but also to decreases in physical and cognitive functioning and may therefore have serious implications on quality of life. Thus, a generic questionnaire, such as the SF-36, seems more appropriate in this situation. The SF-36 is one of the most widely used measures of perceived health status and appeared to be a suitable measure for relatively minor conditions.[18]

The advantage of the QLS^M is that it asks subjects to rate the importance of an item, which probably gives a more accurate evaluation of quality of life.[33] Although the QLS^M-H is a disease-specific module for patients with growth hormone deficiency, we judged that the items in this module, among which questions about body shape, self confidence, ability to become sexually aroused, and physical stamina, are very suitable for the population we studied. There was some overlap in the dimensions of both questionnaires and as to be expected results of both questionnaires were consistent.

We realized that there are questionnaires especially designed for groups of postmenopausal women, like the WHQ[34] and the Specific Quality of Life Questionnaire for Menopause,[35] but there are no validated Dutch versions of these questionnaires available. The questionnaires we chose were judged to provide good alternatives.

There are a few studies assessing effects of hormone therapy (HT) on quality of life in women after menopause. Most of these show positive effects of estrogen supplementation on various parameters of quality of life. The main difference between those studies and the present study is the age of participants. Women in our study are significantly older than women in the HT studies and have consequently been postmenopausal for a longer period of time. This implies that they are less likely to suffer from climacteric symptoms. Some of the HT studies included only women with climacteric symptoms. Relief of those symptoms might positively effect quality of life perception. HT has shown to improve climacteric symptoms.[36–39] Studies enrolling women with climacteric symptoms are therefore more likely to show positive effects of intervention on quality of life than the present study. In the Heart and Estrogen/progestin Replacement Study (HERS) trial, a significant interaction of symptoms of flushing with HT was found and also a positive effect of HT on QoL among women with flushing was seen, whereas HT had adverse effects on QoL of women without menopausal symptoms.[27]

There may be alternative explanations for not finding an effect of the intervention on quality of life, including a so-called response shift.[40] Quality of life may be viewed as the discrepancy between expectations and experience. If an individual has certain expectations of an intervention and the experience of health exceeds those expectations, there is a positive impact on quality of life. However, after a while, one may get used to the new situation and expectations and experience match again. If quality of life measurement takes place after this shift, no quantifiable impact will be measured.

There may also be a ceiling effect for the questionnaires, making it difficult to identify improvement in subjects who already have a good quality of life. We performed a subgroup analysis to obtain evidence for the presence of a ceiling effect. The study population was categorized in two groups based on baseline QoL scores. In the presence of a ceiling effect, an intervention effect may only be present in the subgroup with lower baseline scores, because there we expect the potential to improve QoL. However, no significant difference in change of scores between both intervention

groups in the subgroup with lower baseline scores was found.

In our view, a likely explanation for not finding an effect is that isoflavones do not have the ability to influence quality of life. To the best of our knowledge, there are no studies that have assessed the effect of a soy protein intervention on quality of life in postmenopausal women, but from the literature it is clear that for other endpoints results from both observational studies and intervention studies are far from conclusive. For example, studies on bone mineral density show very contradictory results. Some trials have shown effects of intervention with isoflavones on bone mineral density.[11, 42–44] However, there are also studies that showed no significant effects of isoflavone interventions on bones.[45,46] For hot flushes, data are also confusing, although a recent meta-analysis suggests that there might be an effect of isoflavones that is restricted to women whose initial hot flush frequency was five or more per day.[47] Benefits found in the earliest trials may be chance findings, which is not unlikely because study groups were small and exposure in general short.

CONCLUSION

In conclusion, the findings in the current randomized trial do not support the hypothesis that soy protein containing isoflavones improves quality of life in elderly postmenopausal women.

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REFERENCES

1. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;20:47–63.
2. Hedlund LR, Gallagher JC. The effect of age and menopause on bone mineral density of the proximal femur. *J Bone Miner Res* 1989;44:639–642.
3. Wark JD. Osteoporotic fractures: background and prevention strategies. *Maturitas* 1996;232:193–207.
4. Blumel JE, Castelo-Branco C, Binfa L, et al. Quality of life after the menopause: a population study. *Maturitas* 2000;341:17–23.
5. Ravnikar VA. Compliance with hormone replacement therapy: are women receiving the full impact of hormone replacement therapy preventive health benefits? *Women Health Iss* 1992;22:75–80.
6. Beral V. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52705 women with breast cancer and 108411 women without breast cancer. *Lancet* 1997;350:1047–1059.
7. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;2883:321–333.
8. Grady D, Wenger NK, Herrington D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2000;1329:689–696.
9. Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Female hormones and thrombosis. *Arterioscler Thromb Vasc Biol* 2002; 222:201–210.
10. Albertazzi P, Pansini F, Bonaccorsi G, Zanotti L, Forini E, De Aloysio D. The effect of dietary soy supplementation on hot flushes. *Obstet Gynecol* 1998;911:6–11.
11. Potter SM, Baum JA, Teng HY, Stillman RJ, Shay NF, Erdman JW. Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women. *Am J Clin Nutr* 1998;686: 1375S–1379S.
12. Lydeking-Olsen E, Beck Jensen J, Setchell KD, Damhus M, Holm, Jensen T. Isoflavone-rich soymilk prevents bone loss in the lumbar spine of postmenopausal women: a two-year study. *J Nutr* 2002; 132:581S.
13. Anderson JW, Johnstone BM, Cook Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995;3335:276–282.
14. Goodman MT, Wilkens LR, Hankin JH, Lyu LC, Wu AH, Kolonel LN. Association of soy and fiber consumption with the risk of endometrial cancer. *Am J Epidemiol* 1997;1464:294–306.
15. Ingram D, Sanders K, Kolybaba M, Lopez D. Case-control study of phyto-oestrogens and breast cancer. *Lancet* 1997;350:990–994.
16. Kok L, Kreijkamp-Kaspers S, Grobbee DE, van der Schouw YT. Design and baseline characteristics of a trial on health effects of soy protein with isoflavones in postmenopausal women. *Maturitas* 2004;47:21–29.
17. Klipstein-Grobusch K, den Breeijen JH, Goldbohm RA, et al. Dietary assessment in the elderly: validation of a semiquantitative food frequency questionnaire. *Eur J Clin Nutr* 1998;528:588–596.
18. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992;305:160–164.
19. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;306:473–483.
20. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;5111:1055–1068.
21. van den Beld AW, Lamberts SW. The male climacterium: clinical signs and symptoms of a changing endocrine environment. *Prostate Suppl* 2000;10:2–8.
22. Herschbach P, Henrich G, Strasburger CJ, et al. Development and psychometric properties of a disease-specific quality of life questionnaire for adult patients with growth hormone deficiency. *Eur J Endocrinol* 2001;1453:255–265.
23. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982;171:37–49.
24. Ware JE, Kosinksi M, Keller SD. SF-36 Physical and Mental Health Summary Scales: a user's manual. Boston, MA: The Health Institute, 1994.
25. Rubin DB. *Multiple Imputation for Non Response in Surveys*. New York: Wiley, 1987.
26. Little RA, Rubin DB. *Statistical Analysis With Missing Data*. New York: Wiley, 1987.
27. Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. *JAMA* 2002;2875:591–597.
28. Karlberg J, Mattsson LA, Wiklund I. A quality of life perspective on who benefits from estradiol replacement therapy. *Acta Obstet Gynecol Scand* 1995;745:367–372.

29. Wiklund I, Karlberg J, Mattsson LA. Quality of life of postmenopausal women on a regimen of transdermal estradiol therapy: a double-blind placebo-controlled study. *Am J Obstet Gynecol* 1993;168:824–830.
30. Limouzin-Lamothe MA, Mairon N, Joyce CR, Le Gal M. Quality of life after the menopause: influence of hormonal replacement therapy. *Am J Obstet Gynecol* 1994;1702:618–624.
31. Hilditch JR, Lewis J, Ross AH, et al. A comparison of the effects of oral conjugated equine estrogen and transdermal estradiol-17beta combined with an oral progestin on quality of life in postmenopausal women. *Maturitas* 1996;243:177–184.
32. Huber J, Palacios S, Berglund L, et al. Effects of tibolone and continuous combined hormone replacement therapy on bleeding rates, quality of life and tolerability in postmenopausal women. *BJOG* 2002;1098:886–893.
33. de Haes JC, van Knippenberg FC. The quality of life of cancer patients: a review of the literature. *Soc Sci Med* 1985;208:809–817.
34. Hunter M, Battersby R, Whitehead M. Relationships between psychological symptoms, somatic complaints and menopausal status. *Maturitas* 1986;83:217–228.
35. Hilditch JR, Lewis J, Peter A, et al. A menopause-specific quality of life questionnaire: development and psychometric properties. *Maturitas* 1996;243:161–175.
36. Graser T, Romer T, Wiedey KD, Janaud A. Climodien (estradiol valerate 2 mg plus dienogest 2 mg) is safe and effective in the treatment of postmenopausal complaints. *Climacteric* 2001;44:332–342.
37. Elia D, Tamborini A, Leocmach Y, Chadha-Boreham H. Efficacy and tolerability of a low-dose of Oesclim (25 mcg daily) in the management of symptomatic menopausal women: a French open-label study. *Curr Med Res Opin* 2000;162:94–106.
38. Nand SL, Webster MA, Baber R, Heller GZ. Menopausal symptom control and side-effects on continuous estrone sulfate and three doses of medroxyprogesterone acetate. Ogen/Provera Study Group. *Climacteric* 1998;13:211–218.
39. Rebar RW, Trabal J, Mortola J. Low-dose esterified estrogens (0.3 mg/day): long-term and short-term effects on menopausal symptoms and quality of life in postmenopausal women. *Climacteric* 2000;33:176–182.
40. Carr AJ, Gibson B, Robinson PG. Measuring quality of life: Is quality of life determined by expectations or experience? *BMJ* 2001;322:1240–1243.
41. Deleted in proof.
42. Alekel DL, Germain AS, Peterson CT, Hanson KB, Stewart JW, Toda T. Isoflavone-rich soy protein isolate attenuates bone loss in the lumbar spine of perimenopausal women. *Am J Clin Nutr* 2000;723:844–852.
43. Chen YM, Ho SC, Lam SS, Ho SS, Woo JL. Soy isoflavones have a favorable effect on bone loss in Chinese postmenopausal women with lower bone mass: a double-blind, randomized, controlled trial. *J Clin Endocrinol Metab* 2003;8810:4740–4747.
44. Atkinson C, Compston JE, Day NE, Dowsett M, Bingham SA. The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr* 2004;792:326–333.
45. Gallagher JC, Rafferty K, Haynatzka V, Wilson M. The effect of soy protein on bone metabolism. *J Nutr* 2000;130:667S.
46. Anderson JJ, Chen X, Boass A, et al. Soy isoflavones: no effects on bone mineral content and bone mineral density in healthy, menstruating young adult women after one year. *J Am Coll Nutr* 2002;215:388–393.
47. Messina M, Hughes C. Efficacy of soyfoods and soybean isoflavone supplements for alleviating menopausal symptoms is positively related to initial hot flush frequency. *J Med Food* 2003;61:1–11.